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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,311	12/22/2004	Roland Martin	4239-64111-05	9128

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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
11/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,311	MARTIN ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8-10,12-14,16,17 and 19-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6, 8-10, 12-14, 16-17, and 19-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/19/2007 has been entered.

2. In the response received on 9/19/2007, the Applicants cancelled claim 11 and added new claims 27-28. Claims 1, 3-6, 8-10, 12-14, 16-17, and 19-28 are currently pending and are the subject of this office action.

Specification

Objection to the specification regarding improperly designated trademarks, as set forth on page 2 of the office action mailed on 8/11/2006 and page 2 of the office action mailed on 3/19/2007, is *withdrawn* in response to Applicants' amendments to the specification to properly identify trademarks.

Claim Objections

1. Objection to claim 14, as set forth on page 2 of the office action mailed on 8/11/2006 and page 2 of the office action mailed on 3/19/2007, is *withdrawn* in response to Applicants' amendments to the claim to recite "wherein the interferon-beta comprises interferon-beta 1a, interferon-beta 1b, or combinations thereof,".

2. Objection to claim 20, as set forth on page 3 of the office action mailed on 8/11/2006 and page 2 of the office action mailed on 3/19/2007, is *withdrawn* in response to Applicants' amendments to the claim to recite "A method of treating multiple sclerosis comprising".

3. Objection to claims 20 and 21, as set forth on pages 2-3 of the office action mailed on 3/19/22007, is *withdrawn* in response to Applicants' amendments to the claims to recite "administering to the subject".

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Rejection of claims 9, 12, 17, 20, and 21 under 35 USC § 112, second paragraph, as being indefinite regarding claimed trademarks, as set forth on page 4 of the office action mailed on 3/19/2007 and page 6 of the office action mailed on 8/11/2006, is *withdrawn* in response to Applicants' amendments to the claims to recite interferon-beta 1b, and arguments that "daclizumab" is the generic name for the antibody marketed under the trademarked name ZENEPAX.

2. Rejection of claims 9, 12, 17, 20, and 21 under 35 USC § 112, second paragraph, as being indefinite regarding insufficient antecedent basis for the limitation "the interleukin-2 receptor antagonist", as set forth on page 4 of the office action mailed on 3/19/2007, is *withdrawn* in response to Applicants' amendments to the claims to delete this limitation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection withdrawn

1. Rejection of claims 1, 3-6, 8-14, 16-17, 19, and 20-26 under 35 USC § 103(a) as being anticipated by the combination of "Study of Zenepax", Khoury *et al*, Paty *et al*, and Jacobs *et al*, as set forth on pages 5-7 of the office action mailed on 3/19/2007 and pages 7-9 of the office action mailed on 8/11/2007, is *withdrawn*.

In the response received on 9/19/2007, the Applicants argue that the "Study of Zenepax" document is a description of a clinical trial to study the safety and effectiveness of Zenepax/daclizumab for the treatment of multiple sclerosis, and does not disclose any results which would teach or suggest that Zenepax/daclizumab can be a safe or effective treatment for multiple sclerosis. Therefore, there is no teaching or suggestion that would provide a person of skill in the art with the motivation to use Zenepax with interferon-beta for treatment of multiple sclerosis. Furthermore, the Applicants have submitted a declaration by Dr. Alice Fong describing the results of a clinical trial which show that administration of daclizumab and interferon-beta provided unexpectedly increased effectiveness in treatment of multiple sclerosis. Therefore, the Applicants argue that claims cannot be obvious in view of these unexpected results.

These arguments have been fully considered. Regarding the Applicants' arguments of unexpected results as asserted by the Dr. Fong affidavit, it is noted that the combined administration of daclizumab and interferon-beta resulted in a decrease in lesions characteristic of multiple sclerosis compared to administration of interferon-beta alone. However, the Applicants' assertion of unexpected results cannot be fully evaluated because the disclosed study did not include patients treated with placebo only, and furthermore, did not include patients treated with only daclizumab. Thus, it is not clear if combined daclizumab and interferon-beta provided increased protection/treatment compared to daclizumab alone. Furthermore, the details of the study, Exhibit A, was not received with the Dr. Fong declaration. It is also noted that a copy of Dr. Fong's *curriculum vitae* was not provided either. Therefore, it is not clear that combined administration of daclizumab and interferon-beta does in fact provide unexpected results.

However, upon further reconsideration, Applicants' arguments regarding the deficiencies of the "Study of Zenepax" document are convincing, and therefore the rejection is withdrawn.

New Grounds of Rejection

2. Claims 1, 3-6, 8-10, 12-14, 16-17, and 19-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakatani *et al* ("Nakatani" - US 5,886,152), in view of Vincenti *et al* ("Vincenti" - New Eng. J. Med, 1998, Vol 338, p. 161-165) in view of Hayosh *et al* ("Hayosh" - J. Immunol. 1987, Vol. 138, p. 3771-3775), and further in view of Paty *et al* ("Paty" - cited in the previous office actions) and Jacobs *et al* ("Jacobs" - cited in the previous office actions).

The claims of the instant invention are drawn to methods of treating multiple sclerosis comprising administration of a therapeutically effective amount of interferon-beta and a therapeutically effective

amount of an antibody that specifically binds the interleukin-2 receptor. The claims are further drawn to administration of interferon-beta-1a and interferon-beta-1b, and an anti-interleukin-2 receptor antibody that is an anti-Tac (CD25) antibody, and specifically daclizumab.

Nakatani discloses a humanized monoclonal antibody that specifically binds the interleukin-2 receptor, B-B10 (column 1, lines 5-12), and- teaches that this antibody is useful for treatment of various diseases, including multiple sclerosis (column 2, lines 22-37). Nakatani is silent regarding treatment of multiple sclerosis by co-administration of this antibody with interferon-beta.

Vincenti discloses a humanized monoclonal antibody, daclizumab, specific for the interleukin-2 receptor, which is useful for preventing T-cell-mediated transplant rejection (see abstract). Vincenti also teaches that administration of daclizumab is not associated with adverse side effects (see abstract and p. 163). Vincenti is silent regarding the use of daclizumab for treatment of multiple sclerosis.

Hayosh teaches that an antibody specific for the interleukin-2 receptor, OX 39, can inhibit transfer of experimental autoimmune encephalomyelitis (EAE), which is an art-recognized model of multiple sclerosis. Specifically, Hayosh describes inhibition of EAE development in healthy rats that had received spleen cells from rats with EAE cultured with myelin basic protein. This transfer of EAE pathology was inhibited when spleen cells from rats with EAE were cultured with myelin basic protein and OX 39, showing that this anti-interleukin-2 receptor antibody could prevent disease in a model for multiple sclerosi (see p. 3772, 1st-2nd columns and Table II). Based on these results, Hayosh suggests the use of anti-interleukin-2 receptor antibodies for in vivo treatment of multiple sclerosis (p. 3774, last paragraph). However, Hayosh is silent regarding the use of interferon-beta for treatment of multiple sclerosis.

Paty and Jacobs teach administration of IFN-β-1b and IFN-β-1a, respectively, to patients suffering from multiple sclerosis. The disclosures of both documents indicate that both IFN-β molecules are effective in treating multiple sclerosis. Paty describes IFN-β-1b-treated patients with decreased brain inflammation, as evidenced by decreases in the number of lesions detected by MRI (abstract, p. 664-665), while Jacobs teaches that IFN-β-1a-treated patients had significantly fewer exacerbations and a decreased number and volume of brain lesions as determined by MRI (abstract). Neither Paty nor Jacobs teach administration of an antibody specific for interleukin-2 receptor.

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was conceived, to combine the teaches of Nakatani, Vincenti, Hayosh, Paty, and Jacobs to practice a method of treating multiple sclerosis by administration of interferon-beta and an antibody specific for the interleukin-2 receptor. The motivation to do so comes from the disclosures of Nakatani and Hayosh,

which suggest the use of anti-interleukin-2 receptor antibodies for treatment of multiple sclerosis (Nakatani) and that anti-interleukin-2 receptor antibodies are capable of inhibiting pathology caused by autoreactive T cells in a model of multiple sclerosis (Hayosh). Thus, a person of skill in the art would know that the pathology associated with multiple sclerosis can be inhibited by blockade of the interleukin-2 receptor, and would also know of antibodies specific for the interleukin-2 receptor, specifically B-B10, OX 39, and daclizumab, that would be useful for treatment of multiple sclerosis.

Further motivation is provided by the teachings of Paty and Jacobs, which teach the use of interferon-beta polypeptides for treatment of multiple sclerosis. Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to co-administer interferon-beta and anti-interleukin-2 receptor antibodies because the molecules are known, or suggested, individually to be effective for treating multiple sclerosis. *In re Kerkhoven* (205 USPQ 1069, CCPA 1980) summarizes:

"It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a combination that is to be used for the very same purpose: the idea of combining them flows logically from their having been individually taught in the prior art."

For these reasons, it would be obvious to one of ordinary skill in the art to practice a method of treating multiple sclerosis, by administering interferon-beta, including interferon-beta-1a or interferon-beta-1b, with an antibody specific for the interleukin-2 receptor, including the anti-Tac antibody known as daclizumab. A skilled artisan would also be motivated to treat different forms of multiple sclerosis, such as relapsing-remitting multiple sclerosis, with combined anti-interleukin-2 receptor antibodies and interferon-beta due to the underlying pathology of autoreactive T cells common to different types of multiple sclerosis, including relapsing-remitting multiple sclerosis. Furthermore, because anti-interleukin-2 receptor antibodies are suggested by Nakatani and Hayosh to be useful for treatment of multiple sclerosis, a person of ordinary skill in the art would be motivated to combine this treatment with interferon-beta in cases where the patient does not respond to interferon-beta. Finally, although the combination of Nakatani, Vincenti, Hayosh, Paty, and Jacobs does not explicitly teach the dosages of interferon-beta polypeptides or anti-interleukin-2 receptor antibodies, or the claimed routes of administration and dosing schedules, one of ordinary skill in the art would have both the motivation and the ability to optimize these parameters in order to practice the most effective method of treatment. MPEP 2144.05 states:

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223, 235, (CCPA 1955).

In the instant case, the general conditions of treating multiple sclerosis by administering interferon-beta and anti-interleukin-2 receptor antibodies is obvious in view of the art represented by the combination of Nakatani, Vincenti, Hayosh, Paty, and Jacobs, as set forth supra. Therefore, it would be obvious to practice the claimed method using the claimed doses, routes of administration, and timing of administration.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 20 *remains rejected* on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 and 29-34 of co-pending application 10/607,598, as set forth on pages 9-10 of the office action mailed on 8/11/2006 and pages 7-8 of the office action mailed on 3/19/2007.

In the response received on 9/19/2007, the Applicants argue that the claims of the instant application recite a method of treating multiple sclerosis comprising administering anti-interluekin-2 receptor and interferon-beta, while the claims of the '598 application are drawn to a method of treatment of multiple sclerosis comprising administering anti-interleukin-2 receptor antibodies in the absence of interferon-beta. Thus, the scope of the claimed subject matter of the two sets of claims is different and the subject matter of the '598 application is patenably distinct from that of the instant application.

These arguments have been fully considered and are not persuasive. As set forth *supra*, it is known in the art, as evidenced by Paty and Jacobs, that administration of interferon-beta polypeptides is therapeutically useful for treatment of multiple sclerosis. Therefore, because the art (Paty and Jacobs) and the '598 application teach molecules which are individually useful for treatment of multiple sclerosis, it would be obvious to one of ordinary skill in the art to combine interferon-beta with the anti-interleukin-2 receptor antibodies disclosed in the '598 application for treatment of multiple sclerosis.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert Landsman/
Primary Examiner, Art Unit 1647